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rs4771122 predicts multiple measures of long-term weight loss after bariatric surgery

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Abstract

We examined the association of 34 single nucleotide polymorphisms with weight loss up to 9.5 years after Roux-en-Y surgery. Participants were enrollees in the NUgene biobank with stored DNA and linked electronic health records. Ninety-five self-identified white participants underwent surgery and had follow-up weights obtained between 1 and 9.5 years after surgery. SNP rs4771122 was the variant most significantly associated with long term weight loss after surgery in a repeated linear mixed model ($p = .004$) of long-term weight loss. In this model, each additional copy of the minor allele was associated with nearly 5 percent greater percentage weight loss. This same SNP was also nominally significantly ($p < .05$) associated with weight loss trajectories, weight loss nadir, and weight loss 2 years after surgery.

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CONFLICT OF INTEREST

Laura Rasmussen-Torvik, no conflict of interest
Abigail S. Baldridge, no conflict of interest
Jennifer A. Pacheco, no conflict of interest
Sharon A Aufox, no conflict of interest
Kwang-Youn A. Kim, no conflict of interest
Jonathan C Silverstein, no conflict of interest
Erwin W Denham, no conflict of interest
Eric Hungness, no conflict of interest
Maureen E Smith, no conflict of interest
Philip Greenland, no conflict of interest

ETHICAL APPROVAL

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research board and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Keywords

Bariatric Surgery; Repeated Measures; Predictors; Long Term Weight Loss; Roux-en-Y gastric bypass; SNP; Obesity GWAS

INTRODUCTION

There is wide variability in weight loss after Roux-en-Y gastric bypass (RYGB) but the reasons for this variability are incompletely understood. Single nucleotide polymorphisms (SNPs) known to be associated with obesity or waist-to-hip ratio (WHR) in genome-wide association studies (GWAS) are logical targets in investigations into genetic contributors to this variation. A few published studies have examined obesity or WHR GWAS SNPs with weight loss after bariatric surgery (1–3) but have either included only a few SNPs, used simplistic statistical methods, or used datasets with limited follow-up. To better understand how these SNPs may contribute to long-term weight loss after RYGB surgery, we examined the association of 34 SNPs with weight loss up to 9.5 years after bariatric surgery using linear mixed methods and several secondary measures of long-term weight loss.

MATERIALS AND METHODS

Participants and data

Participants for this study were drawn from the NUgene biobank; individuals in NUGene were recruited at Northwestern Medicine Clinics or Evanston Northwestern Hospital (now NorthShore University HealthSystem), provided a blood sample for DNA extraction, completed an entrance questionnaire, and gave permission for use of their electronic health records (EHR) in research. Participants in NUGene who had undergone RYGB surgery were identified through International Classification of Diseases -9-9 and Current Procedural Terminology codes. Information about pre- and post-surgical weights were extracted from EHR while demographic data, including race, were obtained from the entrance questionnaire. Details about assembly of the study population and data extraction have been published previously (4). Patients undergoing reoperations and surgical-take downs were excluded.

Genotyping

We sought to genotype all SNPs that reached genome-wide levels of significance in the largest (at the time of genotyping) GWAS of BMI (5) and WHR (6). The iPLEX GOLD procedure was followed for the SNP analysis. Briefly, Sequenom's Assay Design software was used to create five multiplexed reactions for all SNPs of interest. After extending the primers the products were conditioned and spotted onto SpectroChip Arrays. Extended primers were detected by MassArray Analyzer 4 using matrix-assisted laser desorption ionization–time-of-flight (MALDITOF) method. Data was acquired using the TyperAnalyzer Software from Agena Bioscience (formerly Sequenom). During the design phase of the assay, it was determined that some SNPs would not genotype well on the system and the SNAP browser was used to pick suitable proxies in the Caucasian population. All SNPs having genotyping rates below 95% were discarded, as were SNPs

with HWE p-values less than .01. 34 of 46 SNPs passed these quality control filters. The rs numbers of these SNPs are included in a footnote to Table 1.

Outcome Measures

In all models, percent weight lost from surgery ([post-surgical weight values-surgery weight]/surgery weight) was used as it has been suggested this phenotype facilitates the most sensitive identification of novel predictors of surgery-induced weight loss (7). We included all individuals (n=162) who had at least 1 weight observation 1-year after surgery, and subsequently restricted this to genotyped self-reported whites (n=95). Our primary outcome was long term percent weight loss predicted by a linear mixed model. We chose a linear mixed model including repeated measures of weight obtained at least 1 year after bariatric surgery with a random intercept and unstructured covariance matrix. Each SNP was tested individually in an unadjusted linear mixed model with and without an additional test for interaction with time. In recognition of limited power and to replicate earlier studies, we chose to examine multiple secondary measures of weight loss after bariatric surgery, and to prioritize those SNPs having nominally significant ($p < .05$) associations with multiple measures of weight loss. Our secondary outcomes included lowest percent weight loss recorded post-surgery (percent weight loss nadir), percent weight loss at 1 year (weight measure obtained closest to 1 year after surgery in a range of 12–18 months), percent weight loss at 2 years (range 18–30 months), and long term weight loss trajectories estimated by SAS Proc trajectory. We had previously used a semiparametric, group-based mixture model (SAS Proc Traj) to create trajectory models of percent weight loss from one-year post surgery in this study (4). We tested the statistical significance of each SNP against previously calculated trajectory groups using Pearson's Chi-Squared.

After selection of independently associated demographic predictors (gender, surgery age, surgery weight, height, and recruitment center), SNPs were singly included as additional covariates modeled additively, with each additional unit reflecting an additional copy of the minor allele of each SNP. Mixed linear regression models were additionally adjusted for time since surgery and a time*age interaction term.

RESULTS

Demographics

Informed consent was obtained from all individual participants included in the study. Table 1 presents the demographics of the 95 whites with successful genotyping for analysis, both in total, and by rs477112 genotype. The median number of weight observations one-year or more after surgery per participant was 8, and the average length (SD) of follow-up after surgery was 5.6 (2.2) years, with some individuals having as long as 9.5 years of follow up. There were 1634 weight observations in the dataset. Eighty-one (85%) participants were female, reflecting a typical distribution of bariatric surgery patients in the United States.

Obesity and WHR GWAS SNP associations with long term weight loss after bariatric surgery—A table including P-values and beta estimates for the association of all 34 SNPs with our primary and secondary outcomes reflecting long-term weight loss is

available from the authors. No SNP achieved a Bonferroni corrected (.05/34 = .0017) p-value for association with long term weight loss examined in a linear mixed model. SNP rs4771122 achieved the lowest p-value for association with this trait of p = .0035. SNP rs4771122 was also nominally significantly associated with trajectory group membership, nadir percent weight loss, and 2 year percent weight loss. No other SNP was associated with multiple outcomes.

Table 2 presents beta estimates and p-values for the association of rs4771122 with our primary and secondary measures of long-term weight loss. In all cases, additional copies of the minor (G) allele were associated with a larger percentage weight lost, after adjustment for several variables including pre-surgical BMI. As seen in table 1, in this sample, additional copies of the minor (G) allele were also significantly associated with increased pre-surgical weight. We examined the association of rs4771122 with pre-surgical weight, nadir weight loss, 2 year weight loss, long term weight loss by mixed models, and long term weight loss by trajectories in 52 self-identified blacks genotyped for our study and found no significant associations.

CONCLUSION

In our examination of 34 obesity and WHR GWAS SNPs, SNP rs4771122 in an intron of *MTIF3* was the most significantly associated SNP with long term weight loss using repeated measures of weight captured 1–9.5 years after surgery. SNP rs4772211 was also the only SNP to be associated with multiple other measures of weight loss after surgery such as percent weight loss nadir, and long term weight loss trajectory. In our sample this SNP was also nominally associated with BMI at baseline, with the minor allele of the SNP being associated with higher baseline BMI and greater weight loss after surgery. Like most GWAS discoveries to date, the mechanism of action of rs4772211 through *MTIF3* (or another gene in the region) on obesity or weight loss after surgery is unknown.

Several other studies have examined genetic variation identified in obesity GWAS with weight loss after surgery, perhaps in response to one study that found individuals having rare variation in MC4R, an important obesity GWAS peak, to have different amounts of weight loss after gastric bypass (8)). Like similar studies (9), most of the GWAS SNPs examined in this study were not significantly associated with weight loss after RYGB surgery perhaps because of the relatively small effect sizes of these SNPs on obesity (paired with the limited power of this analysis in 95 individuals), or complex gene by environment interactions important in post-surgical weight loss, or because the SNPs may act through pathways other than satiety or basal metabolic rate. No other candidate gene studies examining obesity or WHR GWAS SNPs have genotyped SNP rs4771122 (1–3). Our study did not replicate previous results from some of these studies suggesting significant association between SNPs in FTO and weight loss after surgery (1, 3). Two GWAS studies have been performed examining weight loss after bariatric surgery and neither identified rs4771122 among the top hits. One GWAS study used a very different measure of long terms weight loss, comparing the group with the highest excess percent body weight lost to the group with the lowest percent excess body weight lost (10). However, a second GWAS (9) used percent weight loss at weight nadir, one of our secondary variables and found SNP rs4771122 was

nominally (p = .02) associated with nadir weight loss in the replications sample, but not in the discovery sample. In the replication sample, each copy of the G allele was associated with 2.14 greater percent weight lost at the nadir (compared to 4.72 greater percent weight lost at the nadir in our study) (9). The nominal association of rs4771122 G allele with greater BMI at baseline aligns with the Speilotes et al. (5) obesity GWAS where the G allele was associated with higher BMI, but is dissimilar to a Finnish study of nearly 1000 bariatric surgery patents that did not find rs4771122 and several other obesity GWAS SNPs to be associated with BMI in patients considering bariatric surgery (11).

Strengths of this study include typing of many BMI and WHR SNPs, extended follow up with many weight measures per individual after surgery, the use of advanced statistical techniques to examine associations with weight loss, and the examination of multiple endpoints. Weaknesses include low power, lack of genome-wide genotyping, and lack of independence between multiple examined endpoints. Based on the results of this study, rs4771122 should be included in future, larger examinations of weight loss after bariatric surgery, and, where possible, these studies should be encouraged to incorporate multiple measures of long-term weight loss utilizing linear mixed methods.

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References

1. Still CD, Wood GC, Chu X, Erdman R, Manney CH, Benotti PN, Petrick AT, Strodel WE, Mirshahi UL, Mirshahi T, Carey DJ, Gerhard GS. High Allelic Burden of Four Obesity SNPs Is Associated With Poorer Weight Loss Outcomes Following Gastric Bypass Surgery. Obesity (Silver Spring). 2011 Epub 2011/02/12 oby20113 [pii]. 10.1038/oby.2011.3
2. Kakela P, Jaaskelainen T, Torpstrom J, Ilves I, Venesmaa S, Paakkonen M, Gylling H, Paajanen H, Uusitupa M, Pihlajamaki J. Genetic risk score does not predict the outcome of obesity surgery. Obes Surg. 2014; 24(1):128–33.10.1007/s11695-013-1080-2 [PubMed: 24065439]
3. Sarzynski MA, Jacobson P, Rankinen T, Carlsson B, Sjostrom L, Bouchard C, Carlsson LM. Associations of markers in 11 obesity candidate genes with maximal weight loss and weight regain in the SOS bariatric surgery cases. Int J Obes (Lond). 2010 Epub 2010/08/25 ijo2010166 [pii]. 10.1038/ijo.2010.166
4. Baldridge AS, Pacheco JA, Aufox SA, Kim KA, Silverstein JC, Denham W, Hungness E, Smith ME, Allen NB, Greenland P, Rasmussen-Torvik LJ. Factors Associated With Long-Term Weight Loss Following Bariatric Surgery Using 2 Methods for Repeated Measures Analysis. Am J Epidemiol. 2015 In Press. 10.1093/aje/kwv039
5. Speliotes EK, Willer CJ, Berndt SI, Monda KL, Thorleifsson G, Jackson AU, Allen HL, Lindgren CM, Luan J, Magi R, Randall JC, Vedantam S, Winkler TW, Qi L, Workalemahu T, Heid IM, Steinthorsdottir V, Stringham HM, Weedon MN, Wheeler E, Wood AR, Ferreira T, Weyant RJ, Segre AV, Estrada K, Liang L, Nemesh J, Park JH, Gustafsson S, Kilpelainen TO, Yang J, Bouatia-Naji N, Esko T, Feitosa MF, Kutalik Z, Mangino M, Raychaudhuri S, Scherag A, Smith AV, Welch R, Zhao JH, Aben KK, Absher DM, Amin N, Dixon AL, Fisher E, Glazer NL, Goddard ME, Heard-Costa NL, Hoesel V, Hottenga JJ, Johansson A, Johnson T, Ketkar S, Lamina C, Li S, Moffatt MF, Myers RH, Narisu N, Perry JR, Peters MJ, Preuss M, Ripatti S, Rivadeneira F, Sandholt C, Scott LJ,

Timpson NJ, Tyrer JP, van Wingerden S, Watanabe RM, White CC, Wiklund F, Barlassina C, Chasman DI, Cooper MN, Jansson JO, Lawrence RW, Pellikka N, Prokopenko I, Shi J, Thiering E, Alavere H, Alibrandi MT, Almgren P, Arnold AM, Aspelund T, Atwood LD, Balkau B, Balmforth AJ, Bennett AJ, Ben-Shlomo Y, Bergman RN, Bergmann S, Biebermann H, Blakemore AI, Boes T, Bonnycastle LL, Bornstein SR, Brown MJ, Buchanan TA, Busonero F, Campbell H, Cappuccio FP, Cavalcanti-Proenca C, Chen YD, Chen CM, Chines PS, Clarke R, Coin L, Connell J, Day IN, Heijer M, Duan J, Ebrahim S, Elliott P, Elosua R, Eiriksdottir G, Erdos MR, Eriksson JG, Facheris MF, Felix SB, Fischer-Posovszky P, Folsom AR, Friedrich N, Freimer NB, Fu M, Gaget S, Gejman PV, Geus EJ, Gieger C, Gjesing AP, Goel A, Goyette P, Grallert H, Grassler J, Greenawalt DM, Groves CJ, Gudnason V, Guiducci C, Hartikainen AL, Hassanali N, Hall AS, Havulinna AS, Hayward C, Heath AC, Hengstenberg C, Hicks AA, Hinney A, Hofman A, Homuth G, Hui J, Igl W, Iribarren C, Isomaa B, Jacobs KB, Jarick I, Jewell E, John U, Jorgensen T, Jousilahti P, Jula A, Kaakinen M, Kajantie E, Kaplan LM, Kathiresan S, Kettunen J, Kinnunen L, Knowles JW, Kolcic I, Konig IR, Koskinen S, Kovacs P, Kuusisto J, Kraft P, Kvaloy K, Laitinen J, Lantieri O, Lanzani C, Launer LJ, Lecoeur C, Lehtimaki T, Lettre G, Liu J, Lokki ML, Lorentzon M, Luben RN, Ludwig B, Manunta P, Marek D, Marre M, Martin NG, McArdle WL, McCarthy A, McKnight B, Meitinger T, Melander O, Meyre D, Midthjell K, Montgomery GW, Morken MA, Morris AP, Mulic R, Ngwa JS, Nelis M, Neville MJ, Nyholt DR, O'Donnell CJ, O'Rahilly S, Ong KK, Oostra B, Pare G, Parker AN, Perola M, Pichler I, Pietilainen KH, Platou CG, Polasek O, Pouta A, Rafelt S, Raitakari O, Rayner NW, Ridderstrale M, Rief W, Ruokonen A, Robertson NR, Rzehak P, Salomaa V, Sanders AR, Sandhu MS, Sanna S, Saramies J, Savolainen MJ, Scherag S, Schipf S, Schreiber S, Schunkert H, Silander K, Sinisalo J, Siscovick DS, Smit JH, Soranzo N, Sovio U, Stephens J, Surakka I, Swift AJ, Tammesoo ML, Tardif JC, Teder-Laving M, Teslovich TM, Thompson JR, Thomson B, Tonjes A, Tuomi T, van Meurs JB, van Ommen GJ, Vatin V, Viikari J, Visvikis-Siest S, Vitart V, Vogel CI, Voight BF, Waite LL, Wallaschofski H, Walters GB, Widen E, Wiegand S, Wild SH, Willemsen G, Witte DR, Witteman JC, Xu J, Zhang Q, Zgaga L, Ziegler A, Zitting P, Beilby JP, Farooqi IS, Hebebrand J, Huikuri HV, James AL, Kahonen M, Levinson DF, Macciardi F, Nieminen MS, Ohlsson C, Palmer LJ, Ridker PM, Stumvoll M, Beckmann JS, Boeing H, Boerwinkle E, Boomsma DI, Caulfield MJ, Chanock SJ, Collins FS, Cupples LA, Smith GD, Erdmann J, Froguel P, Gronberg H, Gyllensten U, Hall P, Hansen T, Harris TB, Hattersley AT, Hayes RB, Heinrich J, Hu FB, Hveem K, Illig T, Jarvelin MR, Kaprio J, Karpe F, Khaw KT, Kiemeney LA, Krude H, Laakso M, Lawlor DA, Metspalu A, Munroe PB, Ouwehand WH, Pedersen O, Penninx BW, Peters A, Pramstaller PP, Quertermous T, Reinehr T, Rissanen A, Rudan I, Samani NJ, Schwarz PE, Shuldiner AR, Spector TD, Tuomilehto J, Uda M, Uitterlinden A, Valle TT, Wabitsch M, Waeber G, Wareham NJ, Watkins H, Wilson JF, Wright AF, Zillikens MC, Chatterjee N, McCarroll SA, Purcell S, Schadt EE, Visscher PM, Assimes TL, Borecki IB, Deloukas P, Fox CS, Groop LC, Haritunians T, Hunter DJ, Kaplan RC, Mohlke KL, O'Connell JR, Peltonen L, Schlessinger D, Strachan DP, van Duijn CM, Wichmann HE, Frayling TM, Thorsteinsdottir U, Abecasis GR, Barroso I, Boehnke M, Stefansson K, North KE, McCarthy MI, Hirschhorn JN, Ingelsson E, Loos RJ. Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index. Nat Genet. 2010; 42(11):937–48. Epub 2010/10/12 ng.686 [pii]. 10.1038/ng.686 [PubMed: 20935630]

6. Heid IM, Jackson AU, Randall JC, Winkler TW, Qi L, Steinthorsdottir V, Thorleifsson G, Zillikens MC, Speliotes EK, Magi R, Workalemahu T, White CC, Bouatia-Naji N, Harris TB, Berndt SI, Ingelsson E, Willer CJ, Weedon MN, Luan J, Vedantam S, Esko T, Kilpelainen TO, Kutalik Z, Li S, Monda KL, Dixon AL, Holmes CC, Kaplan LM, Liang L, Min JL, Moffatt MF, Molony C, Nicholson G, Schadt EE, Zondervan KT, Feitosa MF, Ferreira T, Allen HL, Weyant RJ, Wheeler E, Wood AR, Estrada K, Goddard ME, Lettre G, Mangino M, Nyholt DR, Purcell S, Smith AV, Visscher PM, Yang J, McCarroll SA, Nemesh J, Voight BF, Absher D, Amin N, Aspelund T, Coin L, Glazer NL, Hayward C, Heard-Costa NL, Hottenga JJ, Johansson A, Johnson T, Kaakinen M, Kapur K, Ketkar S, Knowles JW, Kraft P, Kraja AT, Lamina C, Leitzmann MF, McKnight B, Morris AP, Ong KK, Perry JR, Peters MJ, Polasek O, Prokopenko I, Rayner NW, Ripatti S, Rivadeneira F, Robertson NR, Sanna S, Sovio U, Surakka I, Teumer A, van Wingerden S, Vitart V, Zhao JH, Cavalcanti-Proenca C, Chines PS, Fisher E, Kulzer JR, Lecoeur C, Narisu N, Sandholt C, Scott LJ, Silander K, Stark K, Tammesoo ML, Teslovich TM, Timpson NJ, Watanabe RM, Welch R, Chasman DI, Cooper MN, Jansson JO, Kettunen J, Lawrence RW, Pellikka N, Perola M, Vandenput L, Alavere H, Almgren P, Atwood LD, Bennett AJ, Biffar R, Bonnycastle LL, Bornstein

SR, Buchanan TA, Campbell H, Day IN, Dei M, Dorr M, Elliott P, Erdos MR, Eriksson JG, Freimer NB, Fu M, Gaget S, Geus EJ, Gjesing AP, Grallert H, Grassler J, Groves CJ, Guiducci C, Hartikainen AL, Hassanali N, Havulinna AS, Herzig KH, Hicks AA, Hui J, Igl W, Jousilahti P, Jula A, Kajantie E, Kinnunen L, Kolcic I, Koskinen S, Kovacs P, Kroemer HK, Krzelj V, Kuusisto J, Kvaloy K, Laitinen J, Lantieri O, Lathrop GM, Lokki ML, Luben RN, Ludwig B, McArdle WL, McCarthy A, Morken MA, Nelis M, Neville MJ, Pare G, Parker AN, Peden JF, Pichler I, Pietilainen KH, Platou CG, Pouta A, Ridderstrale M, Samani NJ, Saramies J, Sinisalo J, Smit JH, Strawbridge RJ, Stringham HM, Swift AJ, Teder-Laving M, Thomson B, Usala G, van Meurs JB, van Ommen GJ, Vatin V, Volpato CB, Wallaschofski H, Walters GB, Widen E, Wild SH, Willemsen G, Witte DR, Zgaga L, Zitting P, Beilby JP, James AL, Kahonen M, Lehtimaki T, Nieminen MS, Ohlsson C, Palmer LJ, Raitakari O, Ridker PM, Stumvoll M, Tonjes A, Viikari J, Balkau B, Ben-Shlomo Y, Bergman RN, Boeing H, Smith GD, Ebrahim S, Froguel P, Hansen T, Hengstenberg C, Hveem K, Isomaa B, Jorgensen T, Karpe F, Khaw KT, Laakso M, Lawlor DA, Marre M, Meitinger T, Metspalu A, Midthjell K, Pedersen O, Salomaa V, Schwarz PE, Tuomi T, Tuomilehto J, Valle TT, Wareham NJ, Arnold AM, Beckmann JS, Bergmann S, Boerwinkle E, Boomsma DI, Caulfield MJ, Collins FS, Eiriksdottir G, Gudnason V, Gyllensten U, Hamsten A, Hattersley AT, Hofman A, Hu FB, Illig T, Iribarren C, Jarvelin MR, Kao WH, Kaprio J, Launer LJ, Munroe PB, Oostra B, Penninx BW, Pramstaller PP, Psaty BM, Quertermous T, Rissanen A, Rudan I, Shuldiner AR, Soranzo N, Spector TD, Syvanen AC, Uda M, Uitterlinden A, Volzke H, Vollenweider P, Wilson JF, Witteman JC, Wright AF, Abecasis GR, Boehnke M, Borecki IB, Deloukas P, Frayling TM, Groop LC, Haritunians T, Hunter DJ, Kaplan RC, North KE, O'Connell JR, Peltonen L, Schlessinger D, Strachan DP, Hirschhorn JN, Assimes TL, Wichmann HE, Thorsteinsdottir U, van Duijn CM, Stefansson K, Cupples LA, Loos RJ, Barroso I, McCarthy MI, Fox CS, Mohlke KL, Lindgren CM. Meta-analysis identifies 13 new loci associated with waist-hip ratio and reveals sexual dimorphism in the genetic basis of fat distribution. Nat Genet. 2010; 42(11):949–60. Epub 2010/10/12 ng.685 [pii]. 10.1038/ng.685 [PubMed: 20935629]

7. Hatoum IJ, Kaplan LM. Advantages of percent weight loss as a method of reporting weight loss after Roux-en-Y gastric bypass. Obesity (Silver Spring). 2013; 21(8):1519–25.10.1002/oby.20186 [PubMed: 23670991]
8. Mirshahi UL, Still CD, Masker KK, Gerhard GS, Carey DJ, Mirshahi T. The MC4R(I251L) allele is associated with better metabolic status and more weight loss after gastric bypass surgery. J Clin Endocrinol Metab. 2011; 96(12):E2088–96. Epub 2011/10/07. 10.1210/jc.2011-1549 [PubMed: 21976721]
9. Hatoum IJ, Greenawalt DM, Cotsapas C, Daly MJ, Reitman ML, Kaplan LM. Weight loss after gastric bypass is associated with a variant at 15q26.1. Am J Hum Genet. 2013; 92(5):827–34.10.1016/j.ajhg.2013.04.009 [PubMed: 23643386]
10. Rinella ES, Still C, Shao Y, Wood GC, Chu X, Salerno B, Gerhard GS, Ostrer H. Genome-wide association of single-nucleotide polymorphisms with weight loss outcomes after Roux-en-Y gastric bypass surgery. J Clin Endocrinol Metab. 2013; 98(6):E1131–6.10.1210/jc.2012-3421 [PubMed: 23633212]
11. Magi R, Manning S, Yousseif A, Pucci A, Santini F, Karra E, Querci G, Pelosini C, McCarthy MI, Lindgren CM, Batterham RL. Contribution of 32 GWAS-identified common variants to severe obesity in European adults referred for bariatric surgery. PLoS One. 2013; 8(8):e70735.10.1371/journal.pone.0070735 [PubMed: 23950990]

Table 1

Demographic Features of Patients included in the analysis, by rs4771122

Variable[a]	**White Patients (n=95)**	***Rs4771122 AA (n=65)***	***Rs4771122 AG (n=26)***	***Rs4771122 GG (n=4)***	***p***[b]
Number of Observations per Person, median(IQR)	8 (3–22)	7 (3–20)	16 (6–37)	5 (3–8)	0.0808
Years of Follow Up	5.4 (2.2)	5.2 (2.3)	6.1 (2.1)	4.4 (1.6)	0.1150
Range of Follow Up in Years	1.2 – 9.6	1.2 – 9.6	1.7–9.4	2.5 – 6.1	-
Percent Weight Loss at 1 Year	34.6 (9.3)	32.9 (8.7)	38.2 (9.5)	46.2 (–)[c]	0.0481
Percent Weight Loss at 2 year	36.6 (10.5)	33.7 (8.7)	41.1 (11.7)	52.7 (5.5)	0.0004
Percent Weight Loss at Nadir	38.6 (10.9)	35.8 (9.2)	43.7 (12.4)	51.3 (5.9)	0.0003
Percent Weight Loss at final Observation	32.3 (12.6)	29.2 (10.7)	38.7 (14.0)	42.9 (13.6)	0.0008
Height (in)	65.7 (3.5)	65.9 (3.5)	65.0 (3.4)	66.8 (3.4)	0.4563
Age at Surgery	47.8 (10.9)	47.4 (11.1)	50.0 (10.1)	39.8 (8.8)	0.1901
Weight at Surgery (kg)	137.8 (26.3)	134.5 (22.9)	141.6 (29.1)	166.1 (44.3)	0.0430
Northwestern Hospital, n(%)	74 (77.9)	54 (83.1)	18 (69.2)	2 (50.0)	0.1384
Male, n(%)	14 (14.7)	10 (15.4)	3 (11.5)	1 (25.0)	0.7525

[a] Data are presented as mean(SD) unless otherwise noted.

[b] Tests of association are either ANOVA or non-parametric Kruskal-Wallis test for continuous variables and Pearson's Chi-Square test for categorical variables.

[c] Only one patient had an observation between 1 and 1.5 years of surgery.

The complete list of SNPs successfully genotyped includes rs10150332, rs10195252, rs1055144, rs10767664, rs10938397, rs10968576, rs12444979, rs1294421, rs13107325, rs1514175, rs1555543, rs206936, rs2112347, rs2241423, rs2287019, rs2815752, rs2867125, rs2890652, rs29942, rs3817334, rs4771122, rs4846567, rs4929949, rs543874, rs571312, rs6784615, rs6905288, rs7138803, rs7359397, rs887912, rs9491696, rs9842222, rs987237, and rs9939609.

Table 2

Association of SNP rs4771122 and different measures of weight loss after bariatric surgery

Measure	Effect size	P-value for SNP association
Percent Weight loss 1–9 years after surgery by repeated measures regression[a]	4.87	.004
Percent weight loss at 1 year[b]	3.42	.12
Percent weight loss at 2 years[b]	5.37	.004
Percent weight loss at weight loss nadir[b]	4.71	.009
Trajectories of weight loss by proc traj[c]	Not applicable[c]	.024

[a]Calculated in a linear mixed regression model, with an unstructured covariance matrix to account for repeated measures, adjusted for gender, surgery age, surgery weight, height, time since surgery, the interaction of surgery age and time since surgery, and recruitment center. Effect size represents increase in long-term percentage weight loss per copy of the minor allele of rs4771122.

[b]Calculated in a linear regression model adjusted for gender, surgery age, surgery weight, height, and recruitment center. Effect size represents increase in percentage weight loss (at 1 or 2 years) per copy of the minor allele of rs4771122.

[c]Comparing the distribution of rs477122 genotypes across 4 weight loss trajectories determined by proc traj using a chi-squared test. There is a higher percentage of individuals with the GG genotype in the 2 trajectories indicating higher long term weight loss.

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